The Feasibility of a Short Bevacizumab Infusion in Patients with Metastatic Colorectal Cancer

TETSUJI TERAZAWA[1,3], HITOSHI NISHITANI[1,3], KEN KATO[1], HIRONOBU HASHIMOTO[2], KOHEI AKIYOSHI[1], SATORU IWASA[1], TAKAKO EGUCHI NAKAJIMA[4], TETSUYA HAMAGUCHI[1], YASUHIDE YAMADA[1] and YASUHIRO SHIMADA[1]

[1]*Gastrointestinal Oncology Division, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan;*
[2]*Department of Pharmacy, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan;*
[3]*Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatuki-shi, Osaka, Japan;*
[4]*Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan*

Abstract. *Background: Typically, bevacizumab is initially infused for 90 min, then for 60 min, and subsequently for 30 min. The objective of the present study was to evaluate the safety profile of a short infusion of bevacizumab in Japanese colorectal cancer patients. Patients and Methods: The records of 58 patients who received bevacizumab (5 mg/kg) from June 2010 to September 2010 were reviewed. Bevacizumab was administered for 30 min at the first time. If patients had no infusion reaction, the infusion time was shortened to 10 min. Results: None of the 58 patients who received bevacizumab experienced an infusion reaction (95% confidence interval 0-6.2). The only serious adverse event related to bevacizumab infusion was grade 3 proteinuria in 2 patients. Conclusion: Short infusion of bevacizumab for 30 min the first time and 10 min is safe and feasible.*

Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A), has been approved for the treatment of metastatic colorectal cancer. Bevacizumab in combination with chemotherapy improves overall survival, progression-free survival, and the response rate in patients with metastatic colorectal cancer (1-3). Bevacizumab is now considered standard treatment for metastatic colorectal cancer.

Several monoclonal antibodies, including bevacizumab, trastuzumab, cetuximab, and rituximab, are available for standard therapy; however, all have potential for infusion-related reactions (4-6). The incidence of severe infusion-related reactions for trastuzumab, cetuximab, and rituximab have been reported as <1% (7, 8), 3% (9), and <10% (10, 11), respectively. According to the National Cancer Institute Common Toxicity Criteria (CTC-AE), infusion-related reactions are categorized as hypersensitivity reactions (HSRs) or acute infusion reactions induced by cytokine release (6, 12). In general, infusion reactions are either non-IgE-mediated reactions or allergic reactions to foreign proteins and are classified as type-1 hypersensitivity responses. Non-allergic infusion reactions are complex; some that result from cytokine release are the most predictable side-effects associated with monoclonal antibodies that react with circulating blood cells. Infusion reactions to chimeric and humanized monoclonal antibodies may be a result of their ability to elicit human anti-chimeric antibodies (HACAs) and human anti-human antibodies (HAHAs), respectively (13). Bevacizumab is a monoclonal antibody containing <10% murine protein that is thought to have the potential to induce infusion-related HSRs. Therefore, the standard initial bevacizumab infusion is for 90 min, the second infusion is for 60 min, and all subsequent infusions are for 30 min. Despite the theoretical concern, serious infusion-related HSRs have not been reported in previous bevacizumab-related phase II or III trials (1-3, 14, 15).

However, because of the long infusion time, the standard regimen can be a burden for patients. Although most chemotherapy is performed in an outpatient setting, the regimen needs a great amount of time. Often, cancer patients have to wait for a vacant bed. The standard bevacizumab infusion schedule (90-60-30 min) requires 180 min for the first 3 treatments. In contrast, the short infusion schedule (30-10-10 min) requires only 50 min for the first 3 treatments. Thus, the short infusion schedule saves 130 min for each patient. Short infusions are well-suited to the current state of hospitals for cancer treatment.

Correspondence to: Ken Kato, MD, Ph.D., National Cancer Center Hospital, Gastrointestinal Medical Oncology Division, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel: +81 335422511, Fax: +81 335423815, e-mail: kenkato@ncc.go.jp

Key Words: Bevacizumab, short infusion, feasibility.

The safety of shorter infusions was reported recently (16), and no clinically-significant infusion-related HSRs were reported. Nevertheless, the 90-60-30-min infusion sequence has remained part of the standard administration. However, administration of the longer infusion, which was established without clinical experience, has never been re-assessed. Whether a short infusion of bevacizumab can be administered safely for Japanese patients is unknown. Therefore, we retrospectively investigated the safety of a short infusion of bevacizumab in Japanese patients who were administered bevacizumab at our Institution.

Patients and Methods

Colorectal cancer patients treated with bevacizumab for the first time at our hospital between June 2010 and September 2010 were identified in the NCC database. Medical records including physician office records, nursing records, and chemotherapy treatment records were reviewed and clinical therapy and toxicity data were collected. For the first treatment, bevacizumab (5 mg/kg) was given by intravenous infusion over 30 min. If no infusion reaction occurred, the bevacizumab infusion was given over 10 min followed by FOLFOX or FOLFIRI for all subsequent treatments. Adverse events associated with bevacizumab, such as hypersensitivity, hypertension, proteinuria, periodontitis, gastrointestinal perforation and protracted wound healing, were also evaluated. Characteristics [sex, age and Eastern Cooperative Oncology Group (ECOG) performance status (PS)] and detail of therapy (therapy line, combination chemotherapy, number of medication and total number of infusions) were reviewed.

Toxicity was assessed in all patients receiving at least 2 doses of bevacizumab using CTC-AE v3.0. The 95% confidence interval (CI) of grade 3 or 4 adverse events were calculated using the SPSS version 11 software (SPSS Japan, Tokyo, Japan).

Results

Records of 58 patients who received bevacizumab at the National Cancer Center Hospital between June 2010 and September 2010 were reviewed. The median age was 54 (range=34-77) years; 28 were males and 30 were females. Their PS was as follows: PS 0: 27; PS 1: 28; PS 2: 2; and PS 3: 1. Forty-two patients were administered bevacizumab as first-line treatment; 11, as second-line treatment; and 5, as third-line treatment. Bevacizumab was given with FOLFOX (n=53, 91.3%) or FOLFIRI (n=5, 8.6%). The median number of courses for each patient was 8 (range=2-27), and the total number of 30-min infusions was 58 and the total number of 10-min infusions was 538 (Table I). No HSRs were reported among the 58 patients (95%CI 0-6.2). The toxicities related to bevacizumab were as follows: hypertension grade 1, 3 patients (5%); hypertension grade 2, 7 patients (7%); proteinuria grade 1, 2 patients (3%); proteinuria grade 2, 2 patients (3%); proteinuria grade 3, 2 patients (3%, 95% CI; 0.42-11.91); dental periodontal disease grade 1, 1 patient (1%); and dental periodontal disease grade 2, 1 patient (1%). Gastrointestinal perforation and protracted wound healing were not observed (Table II).

Table I. *Patients' characteristics.*

Characteristic		(%)
Gender		
Male/female	28/30	48/51
Age		
Median (range)	54 (34-77)	
ECOG performance status		
0/1/2/3	27/28/2/1	47/48/3/2
Therapy		
1st/2nd/3rd	42/11/5	72/19/9
Combination chemotherapy		
FOLFOX/FOLFIRI	53/5	91/9
Number of medications		
Median (range)	8 (2-27)	
Total number of infusions		
30 min/10 min	58/538	

Discussion

The present study showed the safety of a short infusion of bevacizumab for Japanese patients. In this study, there were no infusion reactions, gastrointestinal perforations, or wound healing complications. The incidence of toxicities related to bevacizumab, including hypertension, proteinuria, and dental periodontal disease, were similar to those of the standard infusion schedule for bevacizumab (90-60-30 min) (10, 12, 14). The short infusion (30-10-10 min) of bevacizumab was safe and torerable.

Short infusions are well-suited to the current state of cancer treatment hospitals. A total of 60 min can be saved at the first infusion, 50 min at the second infusion, and 20 min at subsequent infusions while treating each patient. The short infusion schedule (30-10-10 min) requires only 50 min for the first 3 treatments. In contrast, the standard infusion schedule for bevacizumab (90-60-30 min) requires 180 min for the first 3 treatments. Most chemotherapy treatments have been administered on an outpatient basis. However, there are a limited number of beds in outpatient chemotherapy Units. The short infusion will reduce the waiting time of outpatients, allowing for more patients to be treated than in the case of standard infusion. Recently, bevacizumab has showed the efficacy widely in the treatment of patients with non-small-cell lung cancer, renal cell cancer and breast cancer (17-24). Colorectal cancer, non-small-cell lung cancer and breast cancer are most common cancer in the world. The use of bevacizumab increases more, and infusion time of bevacizumab becomes more important especially for high volume center. So short time infusion of bevacizumab is meaningful.

Table II. *Toxicity profiles*.

Adverse event CTCAE v3.0	n=58						
	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 3-4	95% CI (grade 3-4)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	%
Infusion reaction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0-6.16
Hypertension	3 (5)	7 (12)	0 (0)	0 (0)	10 (17)	0 (0)	0-6.16
Proteinuria	2 (3)	2 (3)	2 (3)	0 (0)	6 (10)	2 (3)	0.42-11.91
Periodontitis	1 (1)	1 (1)	0 (0)	0 (0)	2 (3)	0 (0)	0-6.16
Gastrointestinal perforation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0-6.16
Protracted wound healing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0-6.16

The present study had certain limitations. Firstly, it was a relatively small retrospective study. However, the feasibility of a short infusion of bevacizumab for metastatic colorectal cancer patients has been reported by Reidy (16). Reidy also reported that use of a standard infusion rate of 0.5 mg/kg/min was safe. This retrospective study demonstrated that the standard (90-60-30 min) infusion of bevacizumab could be changed to 30-10-10 min infusions without serious infusion-related HSRs. This study also supported the safety of short infusion for Japanese patients. Secondly, this study did not assess efficacy. It was not clarified whether there was a difference between standard and short infusion. The initial T1/2 is 1-2 days, and the terminal T1/2 is approximately 14 days; therefore, it appears that efficacy is not associated with infusion time. We plan to confirm whether efficacy is maintained when a short infusion of bevacizumab is administered.

In conclusion, the results of the present study suggest that a short initial infusion of bevacizumab for 30 min, followed by subsequent 10-min infusions, is safe and feasible for Japanese patients. We demonstrated the practical use of a short infusion of bevacizumab at our Institution.

Acknowledgements

We thank Ms. Makiko Shinogi and Ms. Hiromi Orita for data collection. This study was supported by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

References

1 Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, Mass R, Perrou B, Nelson B and Novotny WF: Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol *23*: 3697-3705, 2005.

2 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA and Benson AB, 3rd: Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol *25*: 1539-1544, 2007.

3 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med *350*: 2335-2342, 2004.

4 McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, Jain V, Ho AD, Lister J, Wey K, Shen D and Dallaire BK: Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol *16*: 2825-2833, 1998.

5 Giles FJ, Cortes JE, Halliburton TA, Mallard SJ, Estey EH, Waddelow TA and Lim JT: Intravenous corticosteroids to reduce gemtuzumab ozogamicin infusion reactions. Ann Pharmacother *37*: 1182-1185, 2003.

6 Dillman RO: Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. Cancer metastasis Rev *18*: 465-471, 1999.

7 Herceptin_(trastuzumab) [package insert]. San Francisco, CA: Genentech, Inc., February 2005.

8 Cook-Bruns N: Retrospective analysis of the safety of Herceptin immunotherapy in metastatic breast cancer. Oncology *61(Suppl 2)*: 58-66, 2001.

9 Erbitux (cetuximab) [package insert]. New York, NY: ImClone Systems Incorporated and Princeton, NJ: Bristol-Myers Squibb Company, March 2006.

10 Rituxan (rituximab) [package insert]. San Francisco, CA: Genentech, Inc. and Cambridge, MA: Biogen Idec Inc., February 2006.

11 Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P and Gisselbrecht C: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med *346*: 235-242, 2002.

12 National Cancer Institute. Common Terminology Criteria for Adverse Events v3.0. (CTCAE) Published August 9, 2006. Available at http://ctep.cancer.gov/protocol

13 Lenz HJ: Anti-EGFR mechanism of action: antitumor effect and underlying cause of adverse events. Oncology (Williston Park) *20*: 5-13, 2006.

14 Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF, 3rd, Gaudreault J, Damico LA, Holmgren E and Kabbinavar F: Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol *22*: 2184-2191, 2004.

15 Timoney JP, Eagan MM, and Sklarin NT: Establishing clinical guidelines for the management of acute hypersensitivity reactions secondary to the administration of chemotherapy/ biologic therapy. J Nurs Care Qual *18*: 80-86, 2003.

16 Reidy DL, Chung KY, Timoney JP, Park VJ, Hollywood E, Sklarin NT, Muller RJ and Saltz LB: Bevacizumab 5 mg/kg can be infused safely over 10 minutes. J Clin Oncol *25*: 2691-2695, 2007.

17 Botrel TE, Clark O, Clark L, Paladini L, Faleiros E and Pegoretti B: Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and meta-analysis. Lung cancer *74*: 89-97, 2011.

18 Lima AB, Macedo LT and Sasse AD: Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis. PloS one *6*: e22681, 2011.

19 Miles DW, Chan A, Dirix LY, Cortes J, Pivot X, Tomczak P, Delozier T, Sohn JH, Provencher L, Puglisi F, Harbeck N, Steger GG, Schneeweiss A, Wardley AM, Chlistalla A and Romieu G: Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol *28*: 3239-3247, 2010.

20 Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D and Davidson NE: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med *357*: 2666-2676, 2007.

21 Robert NJ, Dieras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, Perez EA, Yardley DA, Chan SY, Zhou X, Phan SC and O'Shaughnessy J: RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol *29*: 1252-1260, 2011.

22 Rossari JR, Metzger-Filho O, Paesmans M, Saini KS, Gennari A, de Azambuja E and Piccart-Gebhart M: Bevacizumab and Breast Cancer: A Meta-Analysis of First-Line Phase III Studies and a Critical Reappraisal of Available Evidence. Oncology *2012*: 417673, 2012.

23 Sandler AB, Schiller JH, Gray R, Dimery I, Brahmer J, Samant M, Wang LI and Johnson DH: Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small-cell lung cancer treated with Carboplatin and Paclitaxel plus bevacizumab. J Clin Oncol *27*: 1405-1412, 2009.

24 Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, Steinberg SM, Chen HX and Rosenberg SA: A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. The New England journal of medicine *349*: 427-434, 2003.

Received December 4, 2013
Revised January 17, 2014
Accepted January 20, 2014